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10/563,536	06/16/2006	Christian Widmann	KZY-004US	8023

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,536	WIDMANN ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,12,14,15,17-19,23,25 and 27-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *31 and 32* is/are allowed.

6)☒ Claim(s) *1-9,11,12,23,25,27,28 and 33-43* is/are rejected.

7)☒ Claim(s) *14,15,17-19,29 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-9, 11, 12, 14, 15, 17-19, 23, 25 and 27-43 are pending.

Applicants' amendment filed January 25, 2010 is acknowledged. Applicants' response has been fully considered. Claims 1, 2, 9, 12, 27-29, 31, 33, 34, 37, 38, 40 and 41 have been amended. Therefore, claims 1-9, 11, 12, 14, 15, 17-19, 23, 25 and 27-43 are examined.

Abstract

2. A new abstract filed January 25, 2010 is acknowledged.

Withdrawn Claim Objections

3. The previous objection to claims 1-3, 31, 33, 34, 38 and 40-41 regarding sequence identifier "SEQ ID NO:" is withdrawn in view of applicants' amendment to the claims, and applicants' response at page 9 in the amendment filed January 25, 2010.

Withdrawn Claim Rejections - 35 USC § 112

4. The previous rejection of claims 1-9, 11, 12, 14, 15, 17-19, 27-36, 38 and 39 under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 10-12 in the amendment filed January 25, 2010.

5. The previous rejection of claims 1-9, 11, 12, 14, 15, 17-19, 23, 25, 27-36, 38 and 39 under 35 U.S.C. 112, first paragraph, written description, is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 10-12 in the amendment filed January 25, 2010.

6. The previous rejection of claims 9, 12, 23, 27, 28, 33-38 and 40-43 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 12-13 in the amendment filed January 25, 2010.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 23, 25, 37 and 40-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising: i) at least one fragment of the N2 sequence of the RasGAP protein and comprises the amino acid sequence WXWVTXXRTX, wherein X represents an amino acid, and ii) a genotoxin, wherein the at least one peptide enhances the ability of said genotoxin to kill selectively cancer cells; and a method for enhancing sensitivity of a cancer cell to a genotoxin using at least one peptide which is shorter than the N2 sequence of the RasGAP protein and comprises the amino acid sequence WXWVTXXRTX; or a method for treating cancer in a subject using the pharmaceutical composition, does not reasonably provide enablement for a method for enhancing sensitivity of a cancer cell to a genotoxin using at least one peptide which is shorter than the N2 sequence of the RasGAP protein and comprises a variant of the amino acid sequence WXWVTXXRTX; or a method for treating or preventing cancer in a subject using the pharmaceutical composition, wherein the cancer is prevented, or wherein the peptide variant is not defined. The specification

does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 23, 25, 37 and 40-43 are directed to a method for enhancing sensitivity of a cancer cell to a genotoxin using at least one peptide which is shorter than the N2 sequence of the RasGAP protein and comprises the amino acid sequence WXWVTXXRTX or a variant thereof, or a method for treating or preventing cancer in a subject using a pharmaceutical composition comprising a N2 fragment of the RasGAP protein comprising the amino acid sequence WXWVTXXRTX, and a genotoxin. The specification, however, only discloses cursory conclusions (page 3, line 29-page 4, line 7), which state the invention provides a peptide consisting essentially of the N2 sequence of the RasGAP protein, a fragment thereof or a variant thereof, which enhances the ability of a drug to kill selectively cancers cells, and a pharmaceutical composition comprising the peptide. The present application does not provide sufficient teaching/guidance as to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claim is broad and encompasses unspecified variants regarding the peptide variants of N fragment of RasGAP in the method for enhancing sensitivity of a cancer

cell to a genotoxin, and the use of the composition in the method of preventing cancers, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

While Example 2 discloses specific RasGAP N2 fragment potentiates the apoptotic response of tumor cells induced by specific genotoxins such as cisplatin, adriamycin and mitoxantrone (Figs. 1, 2 and 4), the specification does not sufficiently describe the use and effect of peptide variant in enhancing a genotoxin and a method of preventing cancers using a pharmaceutical composition comprising a RasGAP N2 fragment and a genotoxin.

(3). The state of the prior art and relative skill of those in the art:

The art (e.g., Yang *et al.*, Mol. And Cell. Biology 21, 5346-5358 (2001)) teach N1 and N2 fragments of RasGAP sensitizes HeLa cells (a tumor cell) toward DNA induced apoptosis in the presence and absence of cisplatin at various concentrations (see paragraph 13 below). However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the structures of active peptide variants and their use in the method of enhancing sensitivity of a cancer cell to a genotoxin, and a method of preventing cancers using a composition comprising a N2 fragment and a genotoxin to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass the use of variants of N2 fragment of the RasGAP protein in the method for enhancing sensitivity of a cancer cell to a genotoxin, however, the specification does not provide sufficient teachings in the structures of peptide variants and their use in the method for enhancing sensitivity of a cancer cell to a genotoxin. Furthermore, the specification does not

show how the cancer can be prevented by the composition comprising an N2 fragment and a genotoxin, for example, if the cancer does not occur (prevention), how to determine the effect of the composition. Thus, the structures and effects of N2 peptide variants are not predictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for enhancing sensitivity of a cancer cell to a genotoxin using at least one peptide which is shorter than the N2 sequence of the RasGAP protein and comprises a variant of the amino acid sequence WXWVTXXRTX, or a method for treating or preventing cancer in a subject using a pharmaceutical composition comprising a N2 fragment of the RasGAP protein comprising the amino acid sequence WXWVTXXRTX, and a genotoxin. While the specification discloses specific RasGAP N2 fragment enhances the apoptotic response of tumor cells induced by cisplatin, adriamycin and mitoxantrone (Example 2), the specification does not sufficiently describe the use and effect of peptide variants in enhancing various genotoxins and a method of preventing cancers using a pharmaceutical composition comprising a RasGAP N2 fragment and a genotoxin. Furthermore, the specification does not teach how to prevent cancers using the pharmaceutical composition comprising a RasGAP N2 fragment and a genotoxin. Since the specification does not provide sufficient teachings on the structures and effects of active N2 fragment variants in enhancing sensitivity of a cancer cell to a genotoxin, and the method of preventing cancers using the composition, it is necessary to carry out undue experimentation to identify an active N2 fragment variant in enhancing sensitivity of a cancer cell to a genotoxin and to assess the effect of a composition comprising an N2 fragment and a genotoxin in preventing cancers.

(6). Nature of the Invention

The scope of the claim includes a method for treating or preventing cancer in a subject using the pharmaceutical composition, but the specification does not provide sufficient teachings on the use and effect of active N2 fragments in preventing cancers. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed methods associated with variants, the structure and the effect of N2 fragment variant is not predictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to identify an active N2 fragment variants in enhancing sensitivity of a cancer cell to a genotoxin and to assess the effect of a composition comprising an N2 fragment and a genotoxin in preventing cancers.

Response to arguments

Applicants indicate that with respect two terms "or variant thereof" and "preventing cancers" as used in the claims, Applicants have amended the above-cited claims to delete reference to the terms "or variants thereof' and "preventing cancer" for the sole purpose of expediting allowance of the instant application, and not in acquiescence to the Examiner' s allegations that these terms are not enabled by the specification. Thus, this rejection should be withdrawn (page 10 of the response).

Applicants' response has been considered, however, the arguments are not found persuasive because claims 23, 25, 37 and 40-43 still recite one of the two terms. Thus, the rejection is maintained as indicated above.

8. Claim 37 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 37 is directed to a method for enhancing sensitivity of a cancer cell to a genotoxin using at least one peptide which is shorter than the N2 sequence of the RasGAP protein and comprises the amino acid sequence WXWVTXXRTX or a variant thereof.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

While the specification discloses characterization of N2 fragment of RasGAP (residues 158-455), specific fragments containing SH3 domain (residues 284-341) and containing residues 317-326 (SEQ ID NO:4 and 14), which enhances apoptosis of tumor cells in the presence of cisplatin, adriamycin or mitoxantrone (Figs. 1, 2 and 4; Example 2), the specification does not disclose a genus of peptide variants which are shorter than the N2 sequence (298 residues) of the RasGAP protein and comprises variants of the amino acid sequence WXWVTXXRTX that enhance the ability of a genotoxin to kill cancer cells. Some specific fragments of N2 fragment of RasGAP that enhances apoptosis of some genotoxins such as cisplatin, adriamycin and mitoxantrone (Figs. 1, 2 and 4; Example 2) does not provide sufficient written description for the whole genus of N2 peptide variants, since there is substantial variation within the whole genus. The lack description on the N2 peptide variants in the claimed method, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to arguments

Applicants indicate that with respect two terms “or variant thereof” and “preventing cancers” as used in the claims, Applicants have amended the above-cited claims to delete reference to the terms "or variants thereof' and "preventing cancer" for the sole purpose of expediting allowance of the instant application, and not in acquiescence to the Examiner' s allegations that these terms are not enabled by the specification. Thus, this rejection should be withdrawn (page 10 of the response).

Applicants' response has been considered, however, the arguments are not found persuasive because claim 37 still recite the term "or variants thereof'. Thus, the rejection is maintained as indicated above.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 3-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 3 is indefinite because the claim recites the amino acid sequence WMWVTNLRTD as SEQ ID NO:1. However, in the Sequence Listing, SEQ ID NO:1 is a nucleotide sequence, it is not clear what is the sequence identifier for WMWVTNLRTD.

11. Claim 4 is indefinite because of the use of the term "wherein said at least one peptide is in D-form and/or in a retro-inverso isomer form", which does not further limit the scope of claim 1. Claim 1 does not indicate the fragment of the N2 sequence RasGap includes a peptide in D-form and/or in a retro-inverso isomer form.

12. Claims 5-9 are indefinite because of the use of the term "wherein said at least one peptide is conjugated to an agent which increases the cell accumulation of said at least one peptide", which is not encompassed by claim 1. Claims 6-9 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they

depend. Use of the term "wherein said at least one peptide is further conjugated to an agent which increases the cell accumulation of said at least one peptide" is suggested.

Maintained Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-3, 11, 12, 27, 28 and 33-39 are rejected under 35 U.S.C. 102(b) as anticipated by Yang *et al.* (Mol. And Cell. Biology 21, 5346-5358 (2001)) as evidenced by Widmann *et al.* (US 20060234929).

Yan *et al.* teach characterization of RasGAP and its N-fragment (residues 1-455), where N-fragment contain N1 fragment (residues 1-157) and N2 fragment (residues 158-455), which contains 2 SH2 and one SH3 domain (Fig.1; page 5348, right column), and SH3 contains WXWVTXXRTX or SEQ ID NO:4 (WMWVTNLRTD) as evidenced by Widmann *et al.* (paragraphs [0069],[0070]; Tables 1 and 2). The reference also teaches N1 and N2 fragments of RasGAP sensitizes HeLa cells (a tumor cell) toward DNA induced apoptosis, where HeLa cells were transfected with plasmid encoding HA-GAP caspase cleavage fragments (i.e., N1 and N2 fragments), and the cells were treated in the presence and absence of cisplatin at various concentrations, it was found that the N fragment, N1 and N2 fragments enhances apoptosis of HeLa cells in the presence of cisplatin (page 5351, left column-page 5352, left column; page 5354; Figs. 7 and 8; claims 1-3, 11, 12, 27, 28 and 33-39).

Response to arguments

Applicants indicate that Yang et al. discloses an N2 fragment of RasGAP consisting of amino acids 158 to 455 that potentiates apoptosis and cell killing in genotoxin-treated tumor cells. However, in contrast to the Examiner's characterization, Yang et al. does not teach that the N2 fragment enhances apoptosis or the ability to selectively kill cancer cells, as particularly claimed in the instant invention. Selective killing of cancer cells cannot be deduced from Yang et al. because their experiments were conducted solely on HeLa cells. Furthermore, Applicants note that the N-fragment of claim 1 (WxVVVTxxRTx ?, should be WXWVTXXRTX) is neither noted nor commented upon in Yang et al.; consequently, this reference does not teach or suggest the claimed peptide WxVVVTxxRTx of the instant invention. Therefore, the rejection should be withdrawn (pages 13-14 of the response).

Applicants' response has been considered, however, the arguments are not found persuasive because of the following reasons. Yang et al. teach that HeLa cells were transfected with plasmid encoding HA-GAP caspase cleavage fragments (i.e., N1 and N2 fragments), and the cells were treated in the presence and absence of cisplatin at various concentrations, thus both the N2 fragment and cisplatin exist in a composition, where the N2 fragment contains one SH3 domain (Fig.1; page 5348, right column), and SH3 contains WXWVTXXRTX (SEQ ID NO:14) or SEQ ID NO:4 (WMWVTNLRTD) as evidenced by Widmann *et al.* (paragraphs [0069],[0070]; Tables 1 and 2). Since Yang et al. teach the same composition (i.e., a composition comprising an N2 fragment containing WXWVTXXRTX and a genotoxin such as cisplatin) as the claimed composition, the N2 fragment would inherently enhance the ability of the genotoxin to kill selectively cancel cells. While Yang et al. do not disclose the N2 fragment contains WXWVTXXRTX (SEQ ID NO:14), Yang et al. indicate the N2 fragment contains one

SH3 domain, which contains WXWVTXXRTX (SEQ ID NO:14) or SEQ ID NO:4 (WMWVTNLRTD) as evidenced by Widmann *et al.* Thus, the rejection is maintained as indicated above.

Claim Objections

14. Claims 14, 15, 17-19, 29 and 30 are objected to because the claims are dependent from a rejected claim.

Conclusion

15. Claims 1-9, 11, 12, 23, 25, 27, 28 and 33-43 are rejected; and claims 14, 15, 17-19, 29 and 30 are objected to. It appears that claims 31-32 are free of art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached at 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK

April 19, 2010